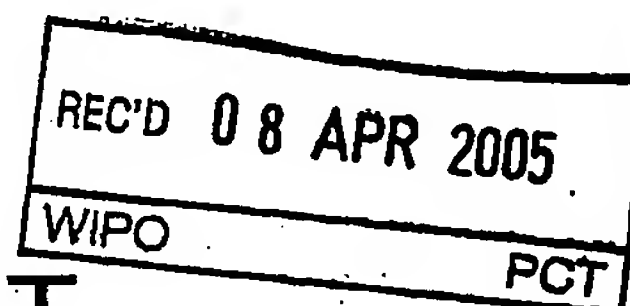


PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY



18/6

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2004/053497

International filing date (day/month/year)
15.12.2004

Priority date (day/month/year)
18.12.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/439, C07D498/08, A61P35/00

Applicant
JANSSEN PHARMACEUTICA N.V.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Telephone No. +49 89 2399-



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/053497

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☐ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:
see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/053497

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial
applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 10

because:

- ☒ the said international application, or the said claims Nos. 10 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/053497

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-12
	No: Claims	
Inventive step (IS)	Yes: Claims	1-10 (part)
	No: Claims	1-10 (part), 11, 12
Industrial applicability (IA)	Yes: Claims	1-9, 11, 12
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item II

Priority

The claimed priority appears not to be valid for part of the claimed subject-matter (e.g. compounds of formula (I) wherein Y represents $-C_{1-2}\text{alkyl-NH-CO-CH}_2R^{15}\text{NH}$, wherein X^1 represents $NR^{16}\text{CO}$ etc.). For said part of the claimed subject-matter P-document D1 is relevant to assess whether the criteria set forth in Article 33(1) PCT are satisfied.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 10 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Prior art

Reference is made to the following documents:

- D1: WO 2004/105765 (P-document)
- D2: WO 03/082290
- D3: WO 98/43960
- D4: J. MED. CHEM. 1997, vol. 40, no. 10, pages 1519-1529
- D5: J. MED. CHEM. 2002, vol. 45, no. 6, pages 1300-1312

2 Novelty (Article 33(2) PCT)

- 2.1 The present compounds of formula (I) are novel over D1-D5 in view of their condensed ring system.
- 2.2 The intermediates claimed in claimed 10 are novel over D1-D5 in view of their quinoline ring substituted in position 3, 4, 6 and 7.

3 Inventive step (Article 33(3) PCT)

3.1 Claims 1-10

The technical problem underlying the present application lies in the provision of further kinase inhibitors useful for treating e.g. cell proliferative disorders. Said problem has been allegedly solved by the present compounds of formula (I). For the purpose of assessing inventive step during the International Preliminary Examination it is assumed that these compounds indeed are kinase inhibitors i.e. solve the above defined technical problem.

For part of the present application which is entitled to the present priority, D2 and D3 represent the closest prior art. D2 and D3 disclose kinase inhibitors which differ however from the present compounds in that they miss the condensed ring system. Accordingly, part of the present application which is entitled to the present priority is based on inventive step.

For part of the present application which is not entitled to the present priority, P-document D1 is regarded as the closest prior art. D1 discloses kinase inhibitors which have a condensed ring system and which are therefore structurally closely related to the present compounds. They appear to differ from the present compounds only in that they have a quinazoline ring instead of a quinoline ring. This structural modification is however clearly anticipated in the prior art (see e.g. D2, definition of X) and hence cannot establish inventive step.

3.2 Claims 11 and 12

Regarding claim 11, the Applicant is reminded that in the case of an analogy process

(i.e. when the process as such is not inventive) an inventive step can be acknowledged for an intermediate only if it makes a structural contribution which differentiates the subsequent product from known compounds of the prior art (i.e. said contribution is responsible for the inventive step of the final product). This is not the case of the intermediates claimed in claim 11 which miss the structural contribution of the compounds (I) i.e. the condensed ring system.

4 Industrial applicability (Article 33(4) PCT)

For the assessment of the present claim 10 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.